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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/540,843	03/31/2000	Barbara A. Gilchrest	0054.1088-015	2644

7590 08/12/2003

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	25

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/540,843	GILCHREST ET AL.	
	Examin r	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *See Continuation Sheet* is/are allowed.

6)☒ Claim(s) *1,3-6,8,14,15,17,19,63,64,77-79,81,85,88,89,93,108 and 109* is/are rejected.

7)☒ Claim(s) *2,16 and 96* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some.* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1-11,13-17,19,20,23,25,26,29,32,51,52,57,58,63,64,69,71,72,75-79,81-83,85,86,88,89,93-96 and 98-113.

Continuation of Disposition of Claims: Claims allowed are 7,9-11,13,20,23,25,26,29,32,51,52,57,58,69,71,72,75,76,82,83,86,94,95,98-107,110-113.

DETAILED ACTION

Non-Final Rejection

Claims 1-11,13-17,19, 20, 23, 25, 26, 29, 32, 51, 52, 57, 58, 63, 64, 69, 71, 72, 75-79, 81-83, 85, 86, 88, 89, 93-96 and 98-113 are pending.

Applicants' traversal, the amendment to claims 2, 7, 14, 26, 75, 85, 88, 93, and 95, the cancellation of claim 97; and the addition of claims 110-113 in paper no. 24 filed on 5/20/03 is acknowledged and considered.

Specification

The use of the trademark AMERICAN TYPE CULTURE COLLECTION (ATCC, Rockville, MD) has been noted in this application on page 21, line 21, page 22, line 20, page 29, line 8. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The use of the trademark COULTER has been noted in this application on page 20, line 18, page 23, line 24 and page 26, line 2. It should be capitalized wherever it appears and be accompanied by the generic terminology.

The use of the trademark AMERSHAM has been noted in this application on page 26, line 25, page 29, line 22, page 31, lines 24 and 26. It should be capitalized wherever it appears and be accompanied by the generic terminology.

The use of the trademark PROMEGA has been noted in this application on page 28, lines 2 and 8, page 30, lines 7, 13, 15, and 23, page 31, lines 7 and 9. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Claim Objections

Claim 2 is objected to as being dependent upon a rejected base claim (claim 1), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 16 is objected to as being dependent upon a rejected base claim (claim 14), but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 96 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 96 does not further limit claim 95 because claim 95 is directed to malignant skin cells and the limitation "skin cells" in claim 96 is broader than malignant skin cells.

Claim Rejections - 35 USC § 112

Applicant's arguments, see paper no. 24, filed on 5/20/03, with respect to 112 first paragraph written description have been fully considered and are persuasive. The rejection of claim 93 has been withdrawn because of the amendment to the claim.

Applicant's arguments, see paper no. 24, filed on 5/20/03, with respect to 112 first paragraph enablement have been fully considered and are persuasive. The rejection of claims14-17, 19, 26, 29, 32, 75-79, 82, 88, 89 and 93, 95, 97 has been withdrawn because of the amendment to the independent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63, 64, 108, and 109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 3, 4, 5, 6, 85, 88, and 89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an effective amount of at least one DNA oligonucleotide, wherein said DNA oligonucleotide is approximately 2-200 nucleotides in length, and wherein the DNA oligonucleotide comprises a phosphodiester backbone in the claimed methods, does not reasonably provide enablement for making and using any oligonucleotide in the claimed methods. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The state of the art for administering oligonucleotides teaches that relatively little is known about the *in vivo* behavior of oligonucleotide (Plenat, Molecular Medicine, Vol. 1, pp. 250-275) and extrapolation from *in vitro* studies to predict pharmacokinetics and effects in a mammal are difficult and inappropriate (abstract). Furthermore, Plenat teaches that, "oligonucleotides in their natural phosphodiester form are subject to rapid degradation in the blood or intracellular fluid by exonuclease and endonucleases (page 250)." In addition, Plenat teaches that oligonucleotides are inhibited from reaching the target by side effects, which result from interactions with cellular or extracellular proteins as well as complementarity with mRNAs for a protein other than the target (page 252).

Furthermore, the art of record further supports the unpredictability of oligonucleotide therapy by displaying conflicting results using the specific oligomer, e.g. TTAGGG (SEQ ID NO: 11 in instant application) for inhibiting cell proliferation. Ohnuma et al. tested the cell growth inhibitory effects of telomere-mimic oligomer, using TTAGGGn, where n=1, 2, 3 or 4 on 8 human tumor cell lines (abstract). Ohnuma displays that only the 18-mer (n=3) and the 24-mer (n=4) inhibited cell growth in some of the cell lines and the 6-mer and 12-mer did not displays any cell growth inhibitory effect (page 2457, table 1). However, Page showed that, "TAG-6 can inhibit telomerase activity *in vitro* and this compound was known to have anti-proliferative effects *in vitro* and *in vivo* against a Burkitt's lymphoma cell line and xenographs in nu/nu C57

black mice (page 41)." In addition, Pages teaches that, "cytotoxicity varies among several types cell types tested with specific cells exhibiting a sensitivity not found in two other types of cell lines (page 47)." Thus, the state of the art teaches that oligonucleotide technology is characterized by a high degree of unpredictability.

The specification provides working examples 1-16 (pages 20-41) a brief description of each example follows.

Examples 1-10 use a dinucleotide pTpT (T2). Examples 1-3 display that using T2 could inhibit different types of cancer cell lines *in vitro*. Examples 4-5 display that using T2 could inhibit different types of normal neonatal cell lines *in vitro*. Example 6 is an *in vivo* comprising topically administering T2 showing that epidermal cell proliferation could be inhibited. Example 7 displays that T2 increases p53 transcription activity in vitro. Example 8 displays that T2 enhances DNA repair via p53 in neonatal human skin cells in vitro. Example 10 displays that T2 induces IL-10 in human keratinocytes, which is likely to cooperate with TNFalpha to inhibit contact hypersensitivity in vitro.

Example 11 uses several different oligonucleotides (SEQ ID NOs: 1, 2, 3, 4, and 6, including T2) and displays that SEQ ID NOs: 1-4 stimulates melanogenesis in human melanocytes *in vitro*. However, SEQ ID NO: 6 did not stimulate melanogenesis in vitro. Example 12 uses T2 and several oligonucleotides (SEQ ID NOs: 5 and 8-12) and displays that SEQ ID NOs: 5, 8, and 10 were highly melanogenic in vitro, while the reverse complimentary sequence of SEQ ID NO: 11 (SEQ NO: 12) were less active (figure 18). However, SEQ ID NOs: 9 and 10 did not produce significant change in pigment content. Furthermore, Example 12 displays that SEQ ID NO: 1 and T2 can penetrate the skin barrier and produce *in vitro* UV-

mimetic effects *in vivo*. In addition, Example 12 displays that oligonucleotide sequence plays a role in determining it melanogenic activity. In addition, Example 12 displays that 5' phosphate is required for efficient uptake.

Example 14 displays that T2 reduced UV-induced mutations *in vivo* and suggest that topical application could be used to lower the mutation rate in carcinogen-exposed skin. Example 15 tested oxidative damage by treating primary newborn fibroblast *in vitro* with T2. The results displayed that T2 increase cell survival. Example 16 tested DNA repair capacity in newborn, young adult, and older adult fibroblast by using either T2 or SEQ ID NO: 1 containing a 5' phosphate. Pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) resulted in up regulated constitutive of UV-induced proteins (p53, p21, XPA, RPA, ERCC/PF, PCNA). In addition, pre-treatment with oligonucleotides (T2 or SEQ ID NO: 1) increased the removal of photoproducts by 30-60 percent.

The specification provides sufficient guidance for using a DNA oligonucleotide, wherein said deoxynucleotides is approximately 2-200 nucleotides in length, and wherein the DNA oligonucleotide comprises a phosphodiester backbone in the claimed methods. However, the breadth of the claims read on using any type of oligonucleotide (DNA, RNA, etc.) and the specification does not provide sufficient guidance for using any RNA oligonucleotide in the claimed methods. The chemical properties and the biological activity of DNA oligonucleotides are distinct from the chemical properties and biological activity of RNA oligonucleotides. The art of record teaches the unpredictability of making and using DNA oligonucleotides and the specification does not provide sufficient guidance to reasonably correlate from making and using the DNA oligonucleotides taught in the specification to making and using any RNA

oligonucleotide embraced by the claimed invention. The art of record is absent for how to make and use RNA oligonucleotides in the claimed method. In view of the lack of guidance provided by the specification for making and using any oligonucleotide in the claimed methods, it would take one skilled in the art an undue amount of experimentation to practice the full scope claimed invention. Thus, the specification does not commensurate with the full scope of the claimed invention.

In addition, with respect to claims 63, 64, and 108-109, the specification does not teach one skilled in the art how to use SEQ ID NOs: 9 or 12 in any medicinal or cosmetic method. The specification provides working examples displaying that several oligonucleotide sequences (SEQ ID NOs: 1, 3, 5, 6, and 11) stimulate melanogenesis in cells *in vitro* (Examples 11 and 12). In addition, the specification provides sufficient guidance showing that SEQ ID NO: 7 (also named SEQ ID NO: 3) and 5 stimulate melanin production in epidermal cells. However, the working examples show that neither SEQ ID NO: 9 nor 12 produce significant change in pigment content. In addition, the chemical structure of SEQ ID NOs: 9 and 12 are distinct compared to either SEQ ID NOs: 5 or 7. The specification does not teach how to use SEQ ID NO: 9 or 12. The art of record does not teach how to use SEQ ID NO: 9 or 12. Thus, the specification does not commensurate with the full scope of the claimed invention.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable making and using an effective amount of at least one DNA oligonucleotide, wherein said DNA oligonucleotide is approximately 2-200 nucleotides in length, and wherein the DNA oligonucleotide comprises a phosphodiester backbone in the claimed methods. Given that

oligonucleotide therapy wherein any oligonucleotide is employed to treat a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to an oligonucleotide therapy effect produced by any oligonucleotide cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of oligonucleotide therapy.

Applicant's arguments with respect to claims 1, 3, 4, 5, 6, 85, 88, and 89 have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments with respect to claims 63, 64, and 108-109 have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments, see paper no. 24, filed on 5/20/03, with respect to 112 second paragraph have been fully considered and are persuasive. The rejection of claims 7 and 14 has been withdrawn because of the amendment to the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77-79 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 77-79 and 81 recite the limitation "DNA fragment". There is insufficient antecedent basis for this limitation in the claims.

Applicant's arguments with respect to claims 77-79 and 81 have been considered but are moot in view of the new ground(s) of rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 5, 6, 8, 14, 15, 17, 19, and 93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 6, 7, 8, 12, 13, 14, 15, 16, 17, 18, and 22 of U.S. Patent No. 5,643,556. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are directed to a method of increasing melanin production in epidermal cells comprising administering DNA fragment to the epidermal cells, wherein the DNA fragment selected from the group consisting of: single-stranded DNA fragments, double-stranded DNA fragments, a mixture of single- and double-stranded DNA fragments, and deoxynucleotides. In addition, both claims are directed to protecting the epidermis of a mammal against ultraviolet damage comprising topically administering to the epidermis DNA fragment to the epidermal cells, wherein the DNA fragment selected from the group consisting of: single-stranded DNA

fragments, double-stranded DNA fragments, a mixture of single- and double-stranded DNA fragments, and deoxynucleotides.

Applicant's arguments with respect to claims 1, 3, 5, 6, 8, 14, 15, 17, 19, and 93 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 3, 6, 14, 15, 19, and 93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 6, and 8 of U.S. Patent No. 5,532,001 (IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are directed to a method of increasing melanin production in epidermal cells comprising administering DNA fragment to the epidermal cells, wherein the DNA fragment selected from the group consisting of: single-stranded DNA fragments, double-stranded DNA fragments, a mixture of single- and double-stranded DNA fragments, and deoxynucleotides.

Applicant's arguments with respect to claims 1, 3, 6, 14, 15, 19, and 93 have been considered but are moot in view of the new ground(s) of rejection.

Claims 8, 14, 15, 19, and 93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 8 of U.S. Patent No. 5,580,547 (IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are directed to administering DNA fragment to the skin, wherein the DNA fragment selected from the group consisting of: single-stranded DNA

fragments, double-stranded DNA fragments, a mixture of single- and double-stranded DNA fragments, and deoxynucleotides.

Applicant's arguments with respect to claims 8, 14, 15, 19, and 93 have been considered but are moot in view of the new ground(s) of rejection.

Claims 14, 15, 19, and 93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 6, and 8 of U.S. Patent No. 5,470,577 (IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are directed to a method of increasing melanin production in epidermal cells comprising administering DNA fragment to the epidermal cells, wherein the DNA fragment is thymidylic acid dinucleotide (pTpT).

Applicant's arguments with respect to claims 14, 15, 19, and 93 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER